

## Online Resource 1

### INTEGRATIVE GENETIC, EPIGENETIC AND PATHOLOGICAL ANALYSIS OF PARAGANGLIOMA REVEALS COMPLEX DYSREGULATION OF NOTCH SIGNALING

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The file contains the following Supplementary Tables: synopsis of the 28 prospectively-sampled paraganglioma cases investigated in the study (**Supplementary Table 1**); table detailing case data, *SDH* mutations and *SDHB* immunohistochemistry (**Supplementary Table 2**); synopsis of the NOTCH1-related immunohistochemical and pathological variables (**Supplementary Table 3**); synopsis of the data concerning the 18 Jacobson's nerve samples that served as controls for RNA and miRNA studies (**Supplementary Table 4**); list of the oligonucleotide sequences used for cloning, qRT-PCR and site direct mutagenesis (**Supplementary Table 5**); list of miRNA mimics used in transfection experiments (**Supplementary Table 6**); list of the genes showing highest concordance for tumor-associated CNVs (**Supplementary Table 7**); list of the most significant functional-related gene groups identified using DAVID (**Supplementary Table 8**); table detailing the fractions of the mutation carriers for the *SDHB*, *SDHC*, *SDHD* and *SDHAF2* genes and of the cases with tumor associated loss of *SDHB* in the subsets of head and neck paragangliomas analyzed for *SDH* germline mutations (**Supplementary Table 9**); table showing the individual characteristics, the fraction with *SDH* mutations and the fraction with loss of *SDHB* immunostaining in the PGL subsets with different clinical presentation (**Supplementary Table 10**); table showing the mean NOTCH1 and JAG2 immunostaining intensities in chief cells, sustentacular cells and endothelial cells of the paraganglioma subsets defined according to *SDH* mutation status and *SDHB* immunohistochemistry (**Supplementary Table 11**).

**Supplementary Table 1 - Synopsis of the 28 prospectively-sampled paraganglioma cases (29 individual tumors) investigated in the present study.** The table details the type(s) of donated sample(s) and the studies performed in relation to the individual and clinico-pathological data. Acronyms include case number, followed by abbreviations referring to paraganglioma (P) localization: PTJ, tympano-jugular; PT, tympanic; PC, carotid body; PV, vagal. #: 5PC and 5PV are distinct paragangliomas originating in the same patient, respectively in the right carotid body and along the left vagus nerve. Bold characters in “Disease localization(s)” indicate the primary tumor analyzed in the current study. na: Fisch classification not applicable. Acronyms for study procedures are detailed in the printed text.

Acronym	Gender	Age (yrs) at surgery	Disease localization(s)	Family history	Modified Fisch class*	Studies
1PTJ	F	25	mediastinal; left vagal, <b>left tympano-jugular</b> (recurrence); left carotid body	yes	C2	CNV, qPCR, miRNA expression profiling, qRT-PCR, IHC
2PTJ	M	59	<b>right tympano-jugular</b>	no	C2	CNV, qPCR, miRNA expression profiling, qRT-PCR, IHC, EM, Cryo-IEM, IF
3PT	F	73	<b>right tympanic</b>	no	A2	CNV, qPCR, miRNA expression profiling, qRT-PCR, IHC
4PTJ	M	42	<b>right tympano-jugular</b>	no	C3	CNV, qPCR, miRNA expression profiling, qRT-PCR, IHC, EM, Cryo-IEM, IF
5PC <sup>#</sup>	F	52	<b>right carotid body</b> ; left tympano-jugular; left vagal	no	na	CNV, qPCR, miRNA expression profiling, qRT-PCR, IHC, EM, Cryo-IEM, IF
5PV <sup>#</sup>	F		right carotid body; left tympano-jugular; <b>left vagal</b>	no	na	CNV, qPCR, miRNA expression profiling, qRT-PCR
6PTJ	F	52	<b>right tympano-jugular</b>	no	C2	CNV, qPCR, miRNA expression profiling, qRT-PCR, IHC, EM, Cryo-IEM, IF
7PC	F	42	<b>right carotid body</b> ; left tympano-jugular	no	na	CNV, qPCR, miRNA expression profiling, qRT-PCR, IHC, EM, Cryo-IEM, IF
8PTJ	M	31	<b>right tympano-jugular</b>	no	C3	CNV, qPCR, IHC, EM, Cryo-IEM, IF
11PT	M	57	<b>left tympanic</b>	no	B3	CNV, qPCR, EM, Cryo-IEM, IF
12PTJ	F	74	<b>left tympano-jugular</b>	no	A2	CNV, qPCR, EM, Cryo-IEM, IF
13PTJ	M	58	<b>right tympano-jugular</b>	no	C3	CNV, qPCR, IHC, EM, CIEM, IF
14PT	M	43	<b>left tympanic</b>	no	A	CNV, qPCR, miRNA expression profiling, qRT-PCR
19PT		74	<b>right tympanic</b>	no	B3	CNV, qPCR
20PT	M	51	<b>right tympanic</b>	no	B3	CNV, qPCR, IHC, EM, Cryo-IEM, IF
21PTJ	M	34	<b>right tympano-jugular</b>	no	C3	CNV, qPCR, miRNA expression profiling, qRT-PCR, IHC
32PT	M	56	<b>right tympanic</b>	no	A2	CNV, qPCR, miRNA expression profiling, qRT-PCR
33PT	F	52	<b>right tympanic</b>	no	B3	CNV, qPCR, miRNA expression profiling, qRT-PCR
34PTJ	F	25	<b>left tympano-jugular</b> (recurrence); metastases in 4/17 regional lymph nodes	no	C2	CNV, qPCR, IHC
36PT	F	60	<b>right tympanic</b>	no	B3	CNV, qPCR, IHC
37PTJ	F	63	<b>right tympano-jugular</b>	no	C1	CNV, qPCR, miRNA expression profiling, IHC, qRT-PCR
43PTJ	F	68	<b>right tympano-jugular</b>	no	C1	CNV, qPCR, IHC, qRT-PCR
44PT	F	51	<b>right tympanic</b>	no	B3	CNV, IHC, qRT-PCR
45PTJ	M	35	<b>left tympano-jugular</b>	no	C3	CNV, qPCR, IHC
54PTJ	M	34	<b>right carotid body</b> ; <b>left tympano-jugular</b>	no	C2	qPCR, IHC, IF, EM, Cryo-IEM
57PTJ	F	41	<b>left tympano-jugular</b>	no	C2	qPCR, IHC, IF, EM, Cryo-IEM
58PTJ	M	43	<b>right tympano-jugular</b>	no	C2	qPCR, IHC, IF, EM, Cryo-IEM
59PTJ	F	53	<b>left tympano-jugular</b>	no	C1	qPCR, IHC, IF, EM, Cryo-IEM
64PTJ	M	33	<b>right tympano-jugular</b>	no	C1	qPCR, qRT-PCR, IHC, IF, EM, Cryo-IEM, cell culture

\*Shin SH, Sivalingam S, De Donato G, Falcioni M, Piazza P, Sanna M. Vertebral artery involvement by tympanojugular paragangliomas: management and outcomes with a proposed addition to the Fisch classification. Audiol Neurotol. 2012;17:92-104.

**Supplementary Table 2 - Case data, SDH mutations and SDHB immunohistochemistry.** The table details 47 tumors from 46 patients, selected for quality/quantity of the paraffin-embedded material and corresponding to those in Supplementary Table 3. Prospective case acronyms include case number followed by abbreviations for paraganglioma (P) localization: PTJ, tympano-jugular; PT, tympanic; PC, carotid body; PV, vagal. Retrospective (R) cases are indicated by the tumor acronym, followed by the last two digits of the year, R for retrospective and case number. PC-06/R15A and PV-06/R15b are independent tumors from one case. na = not available.

Case acronym	Individual and clinical data					Mutational analysis				SDHB IHC
	Age	Gender	Family history	Tumor localization(s)	Multiple/Recurrent	Genes	Mutation type	Mutation nucleotide	Mutation protein	
<u>1PTJ</u>	25	F	yes	PTJ(lt), PV(lt), PC(bil)	yes	undetected				negative
<u>2PTJ</u>	59	M	no	PTJ(rt)	no	undetected				positive
<u>3PT</u>	73	F	no	PT(rt)	no	na				positive
<u>4PTJ</u>	42	M	no	PTJ(rt)	yes	undetected				positive
<u>5PC</u>	52	F	no	PTJ(lt), PV(lt), PC(rt)	yes	SDHD	FS	c.445_448dupATCT	Truncation	negative
<u>6PTJ</u>	52	F	no	PTJ(rt)	no	na				positive
<u>7PC</u>	42	F	no	PTJ(lt), PC(rt)	yes	undetected				negative
<u>8PTJ</u>	31	M	no	PTJ(rt)	no	SDHB	Large deletion/Rearrangement	na	na	negative
<u>13PTJ</u>	58	M	no	PTJ(rt)	no	undetected				positive
<u>20PT</u>	51	M	no	PT(rt)	no	na				positive
<u>21PTJ</u>	34	M	no	PTJ(rt)	no	SDHB	FS	c.575dupT	p.C192L fsX1	negative
<u>34PTJ</u>	25	F	no	PTJ(lt)	yes (metastatic)	SDHB	MS	c.912G>C	G260R	negative
<u>36PT</u>	60	F	no	PT(rt)	no	na				positive
<u>37PTJ</u>	63	F	no	PTJ(rt)	no	na				positive
<u>43PTJ</u>	52	F	no	PTJ(rt)	no	na				positive
<u>44PT</u>	51	F	no	PT(rt)	no	na				negative
<u>45PTJ</u>	39	M	no	PTJ(lt)	no	undetected				positive
<u>54PTJ</u>	34	M	no	PC(rt), PTJ(lt)	yes	na				negative
<u>57PTJ</u>	41	F	no	PTJ(lt)	no	undetected				positive
<u>58PTJ</u>	43	M	no	PTJ(rt)	yes	SDHC	Splice site alteration	c.241+1G>A	Truncation	positive
<u>59PTJ</u>	53	F	no	PTJ(lt)	no	na				positive
<u>64PTJ</u>	33	M	no	PTJ(rt)	no	na				positive

*Continued*

Case acronym	Individual and clinical data					SDHx genes mutational analysis				SDHB IHC
	Age	Gender	Family history	Tumor localization(s)	Multiple/Recurrent	Genes	Mutation type	Mutation nucleotide	Mutation protein	
PTJ-02/R1	44	F	no	PTJ(rt)	no	undetected				positive
PTJ-03/R2	47	F	no	PTJ(lt)	no	undetected				positive
PC-03/R3	31	M	no	PTJ(rt), PC(bil)	yes	SDHD	Large deletion/Rearrangement	5'UTR_exon1_exon 2 del	Truncation	negative
PTJ-04/R4	27	M	no	PTJ(lt)	no	undetected				positive
PTJ-04/R5	31	M	no	PTJ(rt)	no	undetected				negative
PTJ-04/R6	24	M	no	PTJ(rt)	no	SDHAF2	MS	c.232G>C	p.G78A	negative
PTJ-04/R7	67	F	no	PTJ(rt)	no	undetected				positive
PTJ-04/R8	63	F	no	PTJ(lt)	no	undetected				positive
PTJ-04/R9	53	F	no	PTJ(lt)	no	undetected				positive
PTJ-05/R10	32	F	no	PTJ(lt)	no	undetected				negative
PTJ-05/R11	55	F	no	PTJ(rt)	no	undetected				positive
PTJ-05/R12	42	F	no	PTJ(lt)	no	undetected				negative
PTJ-05/R13	44	F	no	PTJ(lt)	no	undetected				negative
PC-06/R14	49	F	no	PTJ(lt), PC(bil)	yes	SDHD	MS	c.242C>T	p.P81L	negative
PC-06/R15a	59	F	na	PV(lt), PC(lt)	yes	SDHD	MS	c.242C>T	p.P81L	negative
PV-06/R15b										
PTJ-06/R16	64	F	no	PTJ(lt)	no	undetected				positive
PTJ-06/R17	55	M	no	PTJ(lt)	no	na				negative
PV-06/R18	27	F	no	PV(rt)	no	SDHB	NS	c.275G>A	p.W47X	negative
PTJ-06/R19	55	M	no	PTJ(lt), PV(lt)	yes	SDHB	MS	c.232G>C	p.G78A	negative
PTJ-06/R20	40	F	no	PTJ(rt)	no	SDHB	Splice site alteration	c.557+1G>A	Truncation	negative
PTJ-08/R21	45	M	no	PTJ(lt)	no	SDHD	MS	c.341A>G	p.Y114C	positive
PTJ-10/R22	37	M	no	PTJ(lt)	no	undetected				na
PTJ-11/R23	45	F	no	PTJ(rt)	no	undetected				positive
PV-11/R24	49	F	no	PV(bil)	yes	SDHD	FS	c.445_448dupATCT	Truncation	negative

Supplementary Table 2

**Supplementary Table 3 - Synopsis of the NOTCH1-related immunohistochemical and pathological variables.** The 47 individual paraffin-embedded tumors from 46 patients correspond to those detailed in Supplementary Table 2, which provides complementary information. The tumors include 22 of the prospectively-collected cases in supplementary Table 1 (with known CNV status at *NOTCH1* and *JAG2*; gain = 3 or more copies, no change = 2 copies), plus 24 archival cases (with 25 tumors, PC-06/R15a and PV-06/R15b are independent tumors from the same patient). Immunostaining results were evaluated both in terms of % positive cells (in brackets), counted in 4 high magnification fields (400x, each field estimated to contain 250-400 cells), and of intensity, scored on a semiquantitative scale (0 = no staining; 1 = weak but definitely positive staining; 2 = moderate staining; 3 = strong staining). Immunostaining for NOTCH1, JAG2, S100 and BCL2 is detailed for the 3 main PGL cell types (chief cells: CC; sustentacular cells: SC; endothelial cells: EC); immunostaining for synaptophysin (SYN) refers to chief and sustentacular cells (CC and SC) together, as these cell types were similarly and strongly labelled (endothelia were negative), immunostaining for vimentin (VIM) to all cell types (chief, sustentacular, endothelial). Ki67 is evaluated in terms of % of positively-stained nuclei (chief and/or sustentacular cells), counted in 4 high magnification fields. Other routinely assessed clinicopathological variables include presence (yes) or absence (no) of vascular invasion, bone infiltration and atypia. Prospective case acronyms include case number followed by abbreviations referring to paraganglioma (P) localization: PTJ, tympano-jugular; PT, tympanic; PC, carotid body; PV, vagal. Retrospective (R) cases are indicated by tumor acronym, followed by the last two digits of the year, R and case number. na = not available. Asterisks in the NOTCH1 and JAG2 CNV columns indicate 3 cases for which CNVs were assessed by qPCR analysis only.

Case acronym	NOTCH1			JAG2			SYN intensity (%)	CGA intensity (%)	S100			VIM intensity (%)	BCL2			Vascular invasion	Bone infiltration	Atypia			
	CNV	IHC intensity (%)		CNV	IHC intensity (%)				CC	SC	EC		IHC intensity (%)		Ki67 positive cells (%)	IHC intensity (%)					
		CC	SC		CC	SC							CC	SC	CC	SC					
1PTJ	3	1 (100)	2 (100)	2 (100)	3	1 (100)	3 (100)	0 (100)	3 (100)	1(70) 2(30)	0 (100)	3 (100)	0 (100)	3 (90)	1	0 (100)	2 (100)	1 (20)	no	no	yes
2PTJ	2	2 (100)	2 (100)	3 (100)	2	1 (100)	1 (100)	0 (100)	2 (100)	0 (100)	2 (20)	3 (5)	0 (100)	2 (100)	1	0 (100)	1 (100)	1 (100)	no	no	no
3PT	3	2 (100)	2 (100)	3 (100)	4	1 (100)	1 (100)	0 (100)	3 (100)	na	1 (100)	3 (100)	0 (100)	3 (100)	1	0 (100)	1 (100)	0 (100)	no	yes	no
4PTJ	3	1 (100)	1 (100)	2 (100)	3	1 (100)	1 (100)	0 (100)	2 (100)	3 (100)	na	na	0 (100)	3 (80)	1	0 (100)	1 (100)	2 (100)	no	yes	yes
5PC	3	2 (100)	2 (100)	3 (100)	3	1 (100)	2 (100)	0 (100)	3 (100)	1 (80) 3(20)	0 (100)	3 (100)	0 (100)	3 (100)	7	0 (100)	1 (100)	1 (100)	no	no	yes
6PTJ	3	2 (100)	3 (100)	2 (100)	3	1 (100)	3 (100)	0 (100)	3 (100)	1 (60) 3(40)	0 (100)	3 (100)	0 (100)	3 (100)	1	0 (100)	2 (100)	1 (100)	no	no	no
7PC	3	1 (100)	1 (100)	2 (100)	3	1 (100)	2 (100)	0 (100)	3 (100)	1 (60) 2(40)	0 (100)	3 (100)	0 (100)	3 (100)	1	0 (100)	1 (100)	1 (100)	no	no	no
8PTJ	3	2 (100)	2 (100)	3 (100)	2	0 (100)	0 (100)	0 (100)	3 (100)	1 (20) 2(80)	3 (100)	3 (100)	0 (100)	3 (100)	1	0 (100)	1 (100)	1 (100)	no	yes	yes
13PTJ	3	2 (100)	2 (100)	3 (100)	2	1 (100)	1 (100)	0 (100)	3 (100)	1 (50) 2(10)	0 (100)	3 (100)	0 (100)	3 (100)	1	1 (100)	2 (100)	1 (100)	no	no	no
20PT	2	3 (100)	3 (100)	3 (100)	3	1 (100)	1 (100)	0 (100)	3 (100)	na	0 (100)	3 (100)	0 (100)	3 (100)	3	0 (100)	2 (100)	0 (100)	no	no	no
21PTJ	3	1 (100)	1 (100)	2 (100)	3	1 (100)	1 (100)	0 (100)	3 (100)	1 (60) 2(40)	0 (100)	3 (100)	0 (100)	1 (30)	3	0 (100)	1 (100)	1 (100)	yes	no	no
34PTJ	3	1 (100)	1 (100)	2 (100)	3	0 (100)	0 (100)	0 (100)	3 (100)	1 (60) 3(40)	0 (100)	3 (100)	0 (100)	3 (100)	2	0 (100)	1 (100)	1 (100)	no	yes	no
36PT	3	2 (100)	3 (100)	3 (100)	3	1 (100)	3 (5)	0 (100)	3 (100)	1 (90) 3(10)	0 (100)	3 (100)	0 (100)	2 (100)	1	0 (100)	1 (100)	1 (100)	no	yes	yes
37PTJ	3	1 (100)	1 (100)	2 (100)	3	1 (100)	2 (100)	0 (100)	3 (100)	1 (80) 3(20)	0 (100)	3 (100)	0 (100)	3 (100)	1	0 (100)	2 (100)	0 (100)	no	no	no
43PTJ	3	3 (100)	3 (100)	3 (100)	2	1 (100)	2 (100)	0 (100)	3 (100)	1 (20) 3(10)	0 (100)	3 (100)	0 (100)	0 (100)	1	0 (100)	2 (100)	1 (40)	no	yes	no
44PT	2	2 (100)	2 (100)	3 (100)	2	2 (100)	2 (100)	0 (100)	3 (100)	1 (20)	2 (100)	3 (100)	0 (100)	3 (100)	1	1 (70) 2 (30)	1 (70) 2 (30)	1 (50)	no	yes	no

Continued

Case acronym	NOTCH1				JAG2				SYN intensity (%)	CGA intensity (%)	S100			VIM intensity (%)	Ki67 positive cells (%)	BCL2			Vascular invasion	Bone infiltration	Atypia					
	CNV	IHC intensity (%)			CNV	IHC intensity (%)					IHC intensity (%)			CC	SC	EC	CC	SC	EC							
		CC	SC	EC		CC	SC	EC			CC	SC	EC				CC	SC	EC							
45PTJ	3	2 (100)	2 (100)	3 (100)	2	na	na	na	na	3 (10)	0 (100)	3 (100)	0 (100)	3 (100)	1	2 (100)	2 (100)	0 (100)	no	yes	no					
54PTJ	2*	2 (100)	2 (100)	3 (100)	2*	na	na	na	3 (100)	na	1 (100)	3 (100)	0 (100)	3 (100)	1	na	na	na	no	yes	no					
57PTJ	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	3 (100)	0 (100)	3 (100)	0 (100)	3 (100)	2	0 (100)	1 (100)	1 (100)	no	no	no					
58PTJ	2*	2 (100)	2 (100)	3 (100)	2*	1 (100)	1 (100)	0 (100)	3 (100)	1 (80) 3 (20)	1 (100)	3 (100)	0 (100)	1 (100)	1	0 (100)	1 (100)	1 (100)	yes	no	yes					
59PTJ	2*	2 (100)	2 (100)	3 (100)	2*	1 (100)	1 (100)	0 (100)	3 (100)	2 (70) 3 (30)	3 (100)	3 (100)	0 (100)	0 (100)	< 1	0 (100)	0 (100)	1 (100)	no	no	no					
64PTJ	2*	2 (100)	2 (100)	3 (100)	3*	1 (100)	1 (100)	0 (100)	na	1 (50) 2 (40)	1 (50)	3 (100)	0 (100)	na	na	na	na	na	no	na	na					
PTJ-02/R1	na	1 (100)	1 (100)	2 (100)	na	0 (100)	1 (100)	0 (100)	2 (100)	1 (80) 2 (20)	0 (100)	3 (100)	0 (100)	3 (100)	1	0 (100)	1 (100)	1 (100)	no	no	no					
PTJ-03/R2	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	2 (100)	2 (40)	1 (100)	2 (100)	0 (100)	2 (100)	< 1	0 (100)	2 (100)	1 (100)	no	yes	no					
PC-03/R3	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	1 (80) 2 (20)	0 (100)	3 (100)	0 (100)	3 (60) 1 (40)	< 1	0 (100)	1 (50)	0 (100)	no	no	yes					
PTJ-04/R4	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	3 (60)	0 (100)	3 (100)	0 (100)	3 (100)	< 1	0 (100)	1 (100)	0 (100)	no	yes	no					
PTJ-04/R5	na	1 (100)	2 (100)	2 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	1 (50) 2 (40)	1 (100)	3 (100)	0 (100)	3 (100)	1	0 (100)	0 (100)	0 (100)	no	no	yes					
PTJ-04/R6	na	2 (100)	3 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	2 (100)	1 (100)	0 (100)	3 (100)	0 (100)	3 (100)	na	0 (100)	1 (100)	1 (100)	no	no	yes					
PTJ-04/R7	na	2 (100)	2 (100)	3 (100)	na	2 (100)	2 (100)	0 (100)	3 (100)	3 (100)	2 (100)	3 (100)	0 (100)	2 (100)	1	0 (100)	1 (100)	1 (100)	no	no	no					
PTJ-04/R8	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	2 (100)	2 (80) 3 (20)	0 (100)	3 (100)	0 (100)	0 (100)	< 1	3 (100)	3 (100)	1 (40)	no	yes	no					
PTJ-04/R9	na	2 (100)	3 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	1 (70) 2 (30)	0 (100)	3 (100)	0 (100)	2 (100)	< 1	0 (100)	1 (100)	0 (100)	no	no	yes					
PTJ-05/R10	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	1 (60) 2 (40)	0 (100)	3 (100)	0 (100)	3 (100)	< 1	0 (100)	1 (10)	0 (100)	no	yes	yes					
PTJ-05/R11	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	1 (25) 2 (5)	0 (100)	3 (100)	0 (100)	2 (100)	< 1	0 (100)	1 (50)	1 (100)	no	yes	no					
PTJ-05/R12	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	2 (100)	3 (30)	0 (100)	3 (100)	0 (100)	3 (100)	2	0 (100)	0 (100)	1 (40)	no	yes	no					
PTJ-05/R13	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	2 (100)	1 (100)	3 (100)	0 (100)	3 (100)	< 1	0 (100)	1 (100)	0 (100)	no	no	no					
PC-06/R14	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	2 (100)	3 (100)	1 (100)	2 (100)	0 (100)	2 (100)	< 1	0 (100)	1 (100)	2 (100)	no	no	yes					
PC-06/R15a	na	2 (100)	2 (100)	3 (100)	na	0 (100)	0 (100)	0 (100)	3 (100)	2 (40) 3 (60)	0 (100)	3 (100)	0 (100)	3 (100)	< 1	0 (100)	1 (100)	1 (100)	no	no	yes					
PV-06/R15b	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	1 (1)	2 (100)	3 (100)	0 (100)	3 (100)	< 1	0 (100)	1 (100)	1 (100)	no	no	yes					
PTJ-06/R16	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	1 (40) 2 (20)	0 (100)	3 (100)	0 (100)	3 (100)	1	0 (100)	1 (100)	1 (100)	no	no	no					
PTJ-06/R17	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	2 (80) 3 (20)	0 (100)	3 (100)	0 (100)	3 (100)	< 1	0 (100)	0 (100)	0 (100)	no	yes	no					
PV-06/R18	na	2 (100)	3 (100)	3 (100)	na	1 (100)	2 (100)	0 (100)	3 (100)	1 (20) 2 (60)	0 (100)	3 (100)	0 (100)	3 (100)	1	0 (100)	1 (100)	1 (100)	no	no	yes					

Supplementary Table 3 continued

Case acronym	NOTCH1				JAG2				SYN intensity (%)	CGA intensity (%)	S100			VIM intensity (%)	Ki67 positive cells (%)	BCL2			Vascular invasion	Bone infiltration	Atypia	
	CNV	IHC intensity (%)			CNV	IHC intensity (%)					CC	SC	EC	CC	SC	EC	CC	SC	EC			
CNV	CC	SC	EC	CNV	CC	SC	EC	CC	SC	EC	CC	SC	EC	CC	SC	EC	CC	SC	EC	Vascular invasion	Bone infiltration	Atypia
<b>PTJ-06/R19</b>	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	2 (100)	3 (100)	0 (100)	3 (100)	0 (100)	1 (70) 2 (30)	1	0 (100)	1 (100)	1 (100)	no	yes	yes	
<b>PTJ-06/R20</b>	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	3 (100)	0 (100)	3 (100)	3 (100)	3 (100)	1	0 (100)	1 (100)	1 (100)	no	yes	yes	
<b>PTJ-08/R21</b>	na	1 (100)	1 (100)	2 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	na	0 (100)	3 (10)	0 (100)	2 (100)	1	0 (100)	1 (100)	2 (100)	no	yes	no	
<b>PTJ-10/R22</b>	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	1 (70) 2 (30)	0 (100)	3 (100)	0 (100)	3 (80)	2	0 (100)	1 (100)	1 (100)	no	yes	yes	
<b>PTJ-11/R23</b>	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	1 (30) 2 (10)	3 (40)	3 (100)	0 (100)	3 (90)	1	0 (100)	1 (100)	0 (100)	no	yes	no	
<b>PV-11/R24</b>	na	2 (100)	2 (100)	3 (100)	na	1 (100)	1 (100)	0 (100)	3 (100)	3 (100)	0 (100)	3 (100)	0 (100)	2 (100)	< 1	0 (100)	1 (60)	2 (60)	no	no	no	

Supplementary Table 3

**Supplementary Table 4 - Synopsis of the 18 control Jacobson's nerve samples.** The Table reports individual and clinico-pathological data, including donor age, gender, disease for which surgery requiring nerve removal was performed, sample type(s) and use(s) in the present study. Due to minute sample sizes and very low concentrations, most RNAs from Jacobson's nerves (JNs) were pooled in sets, each including 2-5 patients (depending on RNA content). Each individual nerve included in pools contributed the same quantity of RNA, (na = not available, other abbreviations as detailed in the printed text).

Acronym	Gender	Age	Disease	Sample	Studies
JN5	F	39	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL6), miRNA expression profiling
JN6	M	40	hemangioma	normal nerve, blood	RNA pool (CTRL6), miRNA expression profiling
JN8	M	41	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL8), miRNA expression profiling
JN9	F	70	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL8), miRNA expression profiling
JN10	F	59	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL10), miRNA expression profiling
JN12	F	61	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL8), miRNA expression profiling
JN14	M	40	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL10), miRNA expression profiling
JN23	F	55	vestibular schwannoma	normal nerve, blood	miRNA expression profiling, qRT-PCR
JN25	M	36	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL21), miRNA expression profiling
JN26	F	59	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL21), miRNA expression profiling
JN27	F	49	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL21), miRNA expression profiling
JN50	M	47	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL21), miRNA expression profiling
JN51	F	41	vestibular schwannoma	normal nerve, blood	RNA pool (CTRL21), miRNA expression profiling
JN44	F	na	vestibular schwannoma	normal nerve, blood	qRT-PCR
JN46	M	65	vestibular schwannoma	normal nerve, blood	qRT-PCR
JN47	F	na	vestibular schwannoma	normal nerve, blood	qRT-PCR
JN48	M	38	vestibular schwannoma	normal nerve, blood	qRT-PCR
JN49	F	na	vestibular schwannoma	normal nerve, blood	qRT-PCR

**Supplementary Table 5** - Oligonucleotide sequences used for cloning, qRT-PCR and site direct mutagenesis.

	<i>Gene</i>	<i>Name</i>	<i>UPL probe*</i>	<i>Sequence</i>
<b>Cloning</b>	NOTCH1	NOTCH1_7745F_X	-	CAACTCGAGCGACCAGAGGAGCCTTTTA
	NOTCH1	NOTCH1_8664R_X	-	CAACTCGAGTGTGTTGCTGGAGCATCTTC
<b>qRT-PCRs primer</b>	NOTCH1	u85_NOTCH1_F	#85	CGCACAAAGGTGTCTCCAG
	NOTCH1	u85_NOTCH1_R	#85	AGGATCAGTGGCGTCGTG
	JAG2	u17_JAG2_F	#17	TGGGACTGGGACAACGATAC
	JAG2	u17_JAG2_R	#17	ATGCGACACTCGCTCGAT
	HES1	u60_HES1_F	#60	GAAGCACCTCCGAAACCT
	HES1	u60_HES1_R	#60	GTCACCTCGTTCATGCACTC
	HES5	u70_HES5_F	#70	TCAGCTACCTGAAGCACAGC
	HES5	u70_HES5_R	#70	TAGTCCTGGTGCAGGCTCTT
	hsa-miR-34b-5p	34b_F	#21	GCGGCCGTTAGGCAGTGTCATT
	hsa-miR-34c-5p	34c_F	#21	GCGGCCGAGGCAGTGTAGTTAG
	hsa-miR-200a-3p	200a_F	#21	GCGGCCGTTAACACTGTCTGGTA
	hsa-miR-200b-3p	200b_F	#21	GCGGCCGTTAATACTGCCGGTA
	hsa-miR-200c-3p	200c_F	#21	GCGGCCGTTAACACTGCCCTC
	hsa-miR-129-3p	129_F	#21	GCGGCCGGAAGCCCTAACCCAA
	hsa-miR-431-5p	431_F	#21	GCGGCCGTTCTGCAGGCCG
<b>Stem loop RT primers</b>	hsa-miR-127-5p	127_F	#21	GCGGCCGCTGAAGCTCAGAGG
	hsa-miR-433	433_F	#21	GCGGCCGATCATGATGGGCTC
	hsa-miR-483-3p	483_F	#21	GCGGCCGTCACTCCCTCCTC
	RNU6B	U6B_F	#21	GCGGCCGCGCAAGGATGACAGC
	Universal R	UniR	#21	GTGCAGGGTCCGAGGT
	hACTB			Applied assay Cat. # 4331182
	hsa-miR-34b-5p	RT_34b-5p	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACCAATCAG
	hsa-miR-34c-5p	RT_34c-5p	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACCGCAATC
	hsa-miR-200a-3p	RT_200a-3p	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACACATCG
	hsa-miR-200b-3p	RT_200b-3p	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACATCATCA
	hsa-miR-200c-3p	RT_200c-3p	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACACTCCATC
	hsa-miR-129-3p	RT_129-3p	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACATACTT
<b>3'UTR site direct mutagenesis</b>	hsa-miR-431-5p	RT_431-5p	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACACTGCATG
	hsa-miR-127-5p	RT_127-5p	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACATCAGA
	hsa-miR-433	RT_433	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACACACCG
	hsa-miR-483-3p	RT_483-3p	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACAAGACG
	RNU6B	RT_U6B	#21	GTTGGCTCTGGTGCAGGGTCCGAGGTATTGCAACCAGAGCCAACAAAAATGG
	NOTCH1	UTR-NOTCH-mut34F	-	ACACAGAACAGTCAGGTTTTATTATATGTAATGTTATCTG
	NOTCH1	UTR-NOTCH-mut34R	-	CAGTACATATAAATAAAAACCTGACTGTTCTGTAAAATAAAAGTAC
	NOTCH1	UTR-NOTCH-mut200F	-	CTTTGTTCAAGGTCTGTATGTAAGTTGTTCGTTG
	NOTCH1	UTR-NOTCH-mut200R	-	ACAACTACATACAGGACCTGCTGAAACAAGATTG

\*Universal Probe Library (Roche Diagnostics)

**Supplementary Table 6** - List of miRNA mimics from Applied Biosystems-Ambion used in transfection experiments.

<b>microRNA</b>	<b>Accession number</b>	<b>miRBase Stem-Loop Accession</b>	<b>miRBase Mature miRNA Accession</b>
hsa-miR-34b-5p	PM10743	MI0000742	MIMAT0000685
hsa-miR-34c-5p	PM11039	MI0000743	MIMAT0000686
hsa-miR-200a-3p	PM10991	MI0000737	MIMAT0000682
hsa-miR-200b-3p	PM10492	MI0000342	MIMAT0000318
hsa-miR-200c-3p	PM11714	MI0000650	MIMAT0000617
NC2	AM17111		

**Supplementary Table 7 - Genes showing highest concordance for tumor-associated CNVs among the tested paraganglioma samples (104 genes with p<0.01).** Gains are in red background, losses in green background. Hyperlinks to gene, chromosomal position, and, where appropriate, protein, are provided.

Gene	Official full name	Chromosome	Losses	Gains	p-value
1 <a href="#">IDUA</a>	<a href="#">iduronidase, alfa-L</a>	<a href="#">4p16.3</a>	0	15	0.000002
2 <a href="#">ARHGEF16</a>	<a href="#">Rho guanine nucleotide exchange factor (GEF) 16</a>	<a href="#">1p36.3</a>	0	13	0.000026
3 <a href="#">FAM173A</a>	<a href="#">family with sequence similarity 173, member A</a>	<a href="#">16p13.3</a>	0	13	0.000026
4 <a href="#">FBXL16</a>	<a href="#">F-box and leucine-rich repeat protein 16</a>	<a href="#">16p13.3</a>	0	13	0.000026
5 <a href="#">MEGF6</a>	<a href="#">multiple EGF-like-domain 6</a>	<a href="#">1p36.3</a>	0	13	0.000026
6 <a href="#">NOTCH1</a>	<a href="#">Neurogenic notch homolog protein 1</a>	<a href="#">9q34.3</a>	0	13	0.000026
7 <a href="#">PRDM16</a>	<a href="#">PR domain containing 16</a>	<a href="#">1p36.23-p33</a>	0	13	0.000026
8 <a href="#">ABCA2</a>	<a href="#">ATP-binding cassette, sub-family A (ABC1), member 2</a>	<a href="#">9q34</a>	0	12	0.000078
9 <a href="#">C9orf142</a>	<a href="#">chromosome 9 open reading frame 142</a>	<a href="#">9q34.3</a>	0	12	0.000078
10 <a href="#">CLIC3</a>	<a href="#">chloride intracellular channel 3</a>	<a href="#">9q34.3</a>	0	12	0.000078
11 <a href="#">COL20A1</a>	<a href="#">collagen, type XX, alpha 1</a>	<a href="#">20q13.33</a>	0	12	0.000078
12 <a href="#">JMDL8</a>	<a href="#">jumonji domain containing 8</a>	<a href="#">16p13.3</a>	0	12	0.000078
13 <a href="#">METRN</a>	<a href="#">meteordin, glial cell differentiation regulator</a>	<a href="#">16p13.3</a>	0	12	0.000078
14 <a href="#">MSLN</a>	<a href="#">mesothelin</a>	<a href="#">16p13.3</a>	0	12	0.000078
15 <a href="#">PLCH2</a>	<a href="#">phospholipase C, eta 2</a>	<a href="#">1p36.32</a>	0	12	0.000078
16 <a href="#">SSTR5</a>	<a href="#">somatostatin receptor 5</a>	<a href="#">16p13.3</a>	0	12	0.000078
17 <a href="#">STUB1</a>	<a href="#">STIP1 homology and U-box containing protein 1, E3 ubiquitin protein ligase</a>	<a href="#">16p13.3</a>	0	12	0.000078
18 <a href="#">WDR24</a>	<a href="#">WD repeat domain 24</a>	<a href="#">16p13.3</a>	0	12	0.000078
19 <a href="#">FAM20C</a>	<a href="#">family with sequence similarity 20, member C</a>	<a href="#">7p22.3</a>	2	15	0.000179
20 <a href="#">ADAM8</a>	<a href="#">ADAM metallopeptidase domain 8</a>	<a href="#">10q26.3</a>	0	11	0.000221
21 <a href="#">ADRA2C</a>	<a href="#">adreno receptor alpha 2C</a>	<a href="#">4p16</a>	0	11	0.000221
22 <a href="#">ARFGAP1</a>	<a href="#">ADP-ribosylation factor GTPase activating protein 1</a>	<a href="#">20q13.33</a>	0	11	0.000221
23 <a href="#">C1QTNF8</a>	<a href="#">C1q and tumor necrosis factor related protein 8</a>	<a href="#">16p13.3</a>	0	11	0.000221
24 <a href="#">CACNA1H</a>	<a href="#">calcium channel, voltage-dependent, T type, alpha 1H subunit</a>	<a href="#">16p13.3</a>	0	11	0.000221
25 <a href="#">CCDC78</a>	<a href="#">coiled-coil domain-containing protein 78</a>	<a href="#">16p13.3</a>	0	11	0.000221
26 <a href="#">CHTF18</a>	<a href="#">CTF18, chromosome transmission fidelity factor 18 homolog (<i>S. cerevisiae</i>)</a>	<a href="#">16p13.3</a>	0	11	0.000221
27 <a href="#">HAGHL</a>	<a href="#">hydroxyacylglutathione hydrolase-like</a>	<a href="#">16p13.3</a>	0	11	0.000221
28 <a href="#">LCNL1</a>	<a href="#">lipocalin-like 1</a>	<a href="#">9q34.3</a>	0	11	0.000221
29 <a href="#">LOC146336</a>	<a href="#">SSTR5 antisense RNA 1 (non-protein coding)</a>	<a href="#">16p13.3</a>	0	11	0.000221
30 <a href="#">MSLNL</a>	<a href="#">mesothelin-like</a>	<a href="#">16p13.3</a>	0	11	0.000221
31 <a href="#">NARFL</a>	<a href="#">nuclear prelamin A recognition factor-like</a>	<a href="#">16p13.3</a>	0	11	0.000221
32 <a href="#">PANK4</a>	<a href="#">pantothenate kinase 4</a>	<a href="#">1p36.32</a>	0	11	0.000221
33 <a href="#">RHBDL1</a>	<a href="#">rhomboid, veinlet-like 1 (<i>Drosophila</i>)</a>	<a href="#">16p13.3</a>	0	11	0.000221
34 <a href="#">RHOT2</a>	<a href="#">ras homolog gene family, member T2</a>	<a href="#">16p13.3</a>	0	11	0.000221

*Continued*

<b>Gene</b>	<b>Official full name</b>
35 <a href="#">RPUSD1</a>	RNA pseudouridylate synthase domain containing 1
36 <a href="#">TMEM41B</a>	trans-membrane protein 41B
37 <a href="#">FGFRL1</a>	fibroblast growth factor receptor-like 1
38 <a href="#">TUBGCP2</a>	tubulin, gamma complex associated protein 2
39 <a href="#">ATAD5</a>	ATPase family, AAA domain containing 5
40 <a href="#">C16orf13</a>	chromosome 16 open reading frame 13
41 <a href="#">FAM195A</a>	family with sequence similarity 195, member A
42 <a href="#">GNG13</a>	guanine nucleotide binding protein (G protein), gamma 13
43 <a href="#">PHACTR4</a>	phosphatase and actin regulator 4
44 <a href="#">WDR90</a>	WD repeat-containing protein 90
45 <a href="#">GALNS</a>	galactosamine (N-acetyl)-6-sulfate sulfatase
46 <a href="#">SAMD11</a>	sterile alpha motif domain containing 11
47 <a href="#">ADAP1</a>	ArfGAP with dual PH domains 1
48 <a href="#">C4orf42</a>	CTBP1 antisense RNA 1 (non-protein coding)
49 <a href="#">CTBP1</a>	C-terminal binding protein 1
50 <a href="#">DVL1</a>	dishevelled, dsh homolog 1 ( <i>Drosophila</i> )
51 <a href="#">GET4</a>	golgi to ER traffic protein 4 homolog ( <i>S. cerevisiae</i> )
52 <a href="#">MIR4326</a>	microRNA 4326
53 <a href="#">MIR662</a>	microRNA 662
54 <a href="#">NMNAT1</a>	nicotinamide nucleotide adenylyl transferase 1
55 <a href="#">RBP7</a>	retinol binding protein 7, cellular
56 <a href="#">SLC26A1</a>	solute carrier family 26 (sulfate transporter), member 1
57 <a href="#">SNN</a>	stannin
58 <a href="#">SYCE1</a>	synaptonemal complex central element protein 1
59 <a href="#">ZFPFM1</a>	zinc finger protein, multitype 1
60 <a href="#">JAG2</a>	jagged 2
61 <a href="#">C19orf23</a>	CIRBP antisense RNA 1 (non-protein coding)
62 <a href="#">C19orf24</a>	chromosome 19 open reading frame 24
63 <a href="#">CIRBP</a>	cold inducible RNA binding protein
64 <a href="#">MIDN</a>	midnolin
65 <a href="#">CPSF3L</a>	cleavage and polyadenylation specific factor 3-like
66 <a href="#">EAPP</a>	E2F-associated phosphoprotein
67 <a href="#">EFNA2</a>	ephrin-A2
68 <a href="#">GLTPD1</a>	glycolipid transfer protein domain containing 1
69 <a href="#">HES5</a>	hairy and enhancer of split 5 ( <i>Drosophila</i> )
70 <a href="#">RXRA</a>	retinoid X receptor, alpha
71 <a href="#">TAS1R3</a>	taste receptor, type 1, member 3

<b>Chromosome</b>	<b>Losses</b>	<b>Gains</b>	<b>p-value</b>
16p13.3	0	11	0.000221
11p15.4	11	0	0.000221
4p16	1	13	0.000257
10q26.3	1	11	0.000257
17q11.2	10	0	0.000600
16p13.3	0	10	0.000600
16p13.3	0	10	0.000600
16p13.3	0	10	0.000600
1p35.3	10	0	0.000600
16p13.3	0	10	0.000600
16q24.3	1	12	0.000699
1p36.33	1	12	0.000699
7p22.3	0	9	0.001559
4p16.3	0	9	0.001559
4p16	0	9	0.001559
1p36	0	9	0.001559
7p22.3	0	9	0.001559
chr 20	0	9	0.001559
16p13.3	0	9	0.001559
1p36.22	9	0	0.001559
1p36.22	9	0	0.001559
4p16.3	0	9	0.001559
16p13	9	0	0.001559
10q26.3	0	9	0.001559
16q24.2	0	9	0.001559
14q32	1	11	0.001797
19p13.3	2	12	0.003351
19p13.3	2	12	0.003351
19p13.3	2	12	0.003351
19p13.3	2	12	0.003351
1p36.33	0	8	0.003898
14q13.1	8	0	0.003898
19p13.3	0	8	0.003898
1p36.33	0	8	0.003898
1p36.32	0	8	0.003898
9q34.3	0	8	0.003898
1p36.33	0	8	0.003898

Supplementary Table 7 continued

<b>Gene</b>	<b>Official full name</b>	<b>Chromosome</b>	<b>Losses</b>	<b>Gains</b>	<b>p-value</b>
72 <a href="#">TPPP</a>	tubulin polymerization promoting protein	5p15.3	0	8	0.003898
73 <a href="#">WDR47</a>	WD repeat domain 47	1p13.3	8	0	0.003898
74 <a href="#">ACAP3</a>	ArfGAP with coiled-coil, ankyrin repeat and PH domains 3	chr 1	1	10	0.004387
75 <a href="#">PUSL1</a>	pseudouridylate synthase-like 1	1p36.33	1	10	0.004387
76 <a href="#">RHPN1</a>	rhophilin, Rho GTPase binding protein 1	8q24.3	1	10	0.004387
77 <a href="#">SCNN1D</a>	sodium channel, non-voltage-gated1, delta subunit	1p36.3-36.2	1	10	0.004387
78 <a href="#">NOC2L</a>	nucleolar complex associated 2 homolog	1p36.33	2	11	0.007841
79 <a href="#">AKIRIN1</a>	akirin 1	1p34.3	7	0	0.009401
80 <a href="#">BRD9</a>	bromo domain containing 9	5p15.33	0	7	0.009401
81 <a href="#">C17orf42</a>	chromosome 17 open reading frame 42	chr 17	7	0	0.009401
82 <a href="#">C9orf139</a>	chromosome 9 open reading frame 139	9q34.3	0	7	0.009401
83 <a href="#">CYP2E1</a>	cytochrome P450, family 2, subfamily E, polypeptide 1	10q24.3-qter	0	7	0.009401
84 <a href="#">DNLZ</a>	DNL-type zinc finger protein	9q34.3	0	7	0.009401
85 <a href="#">DPP8</a>	dipeptidyl-peptidase 8	15q22	7	0	0.009401
86 <a href="#">FUT7</a>	fucosyl transferase 7 (alpha (1,3) fucosyl transferase)	9q34.3	0	7	0.009401
87 <a href="#">GMEB1</a>	glucocorticoid modulatory element binding protein 1	1p35.3	7	0	0.009401
88 <a href="#">GPSM1</a>	G-protein signaling modulator 1	9q34.3	0	7	0.009401
89 <a href="#">IPP</a>	intra-cisternal A particle-promoted polypeptide	1p34-p32	7	0	0.009401
90 <a href="#">KLHL17</a>	kelch-like 17	1p36.33	0	7	0.009401
91 <a href="#">LRRC37A3</a>	leucine rich repeat containing 37, member A3	17q24.1	7	0	0.009401
92 <a href="#">LZIC</a>	leucine zipper and CTNNBIP1 domain containing	1p36.22	7	0	0.009401
93 <a href="#">PLEKHN1</a>	pleckstrin homology domain containing, family N member 1	1p36.33	0	7	0.009401
94 <a href="#">RGS12</a>	regulator of G-protein signaling 12	4p16.3	0	7	0.009401
95 <a href="#">RHBDL2</a>	rhomboid, veinlet-like 2 (Drosophila)	1p34.3	7	0	0.009401
96 <a href="#">SFPQ</a>	splicing factor proline/glutamine-rich	1p34.3	7	0	0.009401
97 <a href="#">SLC6A3</a>	solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	5p15.3	0	7	0.009401
98 <a href="#">SPON2</a>	spondin 2, extracellular matrix protein	4p16.3	0	7	0.009401
99 <a href="#">SPRNP1</a>	shadow of prion protein homolog (zebrafish) pseudogene 1	10q26.3	0	7	0.009401
100 <a href="#">UBE4B</a>	ubiquitination factor E4B	1p36.3	7	0	0.009401
101 <a href="#">ZBTB8A</a>	zinc finger and BTB domain containing 8A	1p35.1	7	0	0.009401
102 <a href="#">ZBTB8OS</a>	zinc finger and BTB domain containing 8 opposite strand	1p35.1	7	0	0.009401
103 <a href="#">ZNF850</a>	zinc finger protein 850	19q13.12	7	0	0.009401
104 <a href="#">ZYG11B</a>	zyg-11 homolog B (C. elegans)	1p32.3	7	0	0.009401

Supplementary Table 7

**Supplementary Table 8 - Most significant enriched biological themes and functional-related gene groups identified using DAVID (<http://david.abcc.ncifcrf.gov>) for the top 104 CNV-affected genes.** The top terms include “Notch signaling pathway”, “mesothelin”, “ArfGap”, “Rhomboid”, “GoLoco”. The table is ordered according to Bonferroni correction. Only the term “Notch signaling pathway” is statistically significant after Bonferroni and Benjamini corrections. Terms containing *NOTCH1* or molecules related to *NOTCH1* signaling are in bold. Notably, 23 of the 48 partially-redundant terms include *NOTCH1* or genes interacting with *NOTCH1* (in bold).

Category	Term	Count	Genes	P Value	Bonferroni	Benjamini
KEGG_PATHWAY	hsa04330:Notch signaling pathway	5	<b>CTBP1, NOTCH1, HES5, JAG2, DVL1</b>	0,00006	0,002	0,002
PIR_SUPERFAMILY	PIRSF030203:mesothelin	2	MSLN, MSLNL	0,00917	0,333	0,333
SMART	SM00105:ArfGap	3	ARFGAP1, ACAP3, ADAP1	0,00766	0,340	0,340
PIR_SUPERFAMILY	PIRSF037470:rhomboid protein	2	RHBDL1, RHBDL2	0,01373	0,456	0,262
PIR_SUPERFAMILY	PIRSF037470:Rhomboid	2	RHBDL1, RHBDL2	0,01373	0,456	0,262
SMART	SM00390:GoLoco	2	RGS12, GPSM1	0,03270	0,834	0,592
GOTERM_MF_FAT	GO:0008060~ARF GTPase activator activity	3	ARFGAP1, ACAP3, ADAP1	0,00838	0,838	0,838
INTERPRO	IPR001164:Arf GTPase activating protein	3	ARFGAP1, ACAP3, ADAP1	0,00892	0,860	0,860
INTERPRO	IPR010335:Pre-pro-megakaryocyte potentiating factor precursor	2	MSLN, MSLNL	0,01018	0,894	0,674
SMART	SM00233:PH	5	ACAP3, PLCH2, ARHGEF16, PLEKHN1, ADAP1	0,04124	0,897	0,531
SMART	SM00504:Ubox	2	UBE4B, STUB1	0,04185	0,901	0,438
SP_PIR_KEYWORDS	alternative splicing	50	<b>JAG2, FAM195A, GET4, ZYG11B, DPP8, BRD9, GMEB1, ARHGEF16, WDR90, WDR47, ACAP3, C16ORF13, HAGHL, CPSF3L, ARFGAP1, RHPN1, PUSL1, ABCA2, PRDM16, STUB1, ZBTB8OS, RGS12, PLCH2, MSLN, GPSM1, SCNN1D, PHACTR4, C17ORF42, SAMD11, UBE4B, SYCE1, ATAD5, TUBGCP2, DVL1, C9ORF142, SFPQ, JMJD8, NARFL, RHOT2, RHBDL1, CHTF18, CACNA1H, WDR24, RHBDL2, PLEKHN1, MEGF6, TMEM41B, CCDC78, COL20A1, ZBTB8A</b>	0,01661	0,925	0,925
GOTERM_MF_FAT	GO:0030695~GTPase regulator activity	7	ARFGAP1, RGS12, ACAP3, RHPN1, ARHGEF16, GPSM1, ADAP1	0,01239	0,932	0,740
GOTERM_MF_FAT	GO:0060589~nucleoside-triphosphatase regulator activity	7	ARFGAP1, RGS12, ACAP3, RHPN1, ARHGEF16, GPSM1, ADAP1	0,01369	0,949	0,629
INTERPRO	IPR017213:Peptidase S54, rhomboid, metazoan	2	RHBDL1, RHBDL2	0,01523	0,965	0,674
UP_SEQ_FEATURE	domain:Arf-GAP	3	ARFGAP1, ACAP3, ADAP1	0,00902	0,976	0,976
GOTERM_MF_FAT	GO:0005096~GTPase activator activity	5	ARFGAP1, RGS12, ACAP3, GPSM1, ADAP1	0,02082	0,989	0,679
GOTERM_BP_FAT	GO:0032312~regulation of ARF GTPase activity	3	ARFGAP1, ACAP3, ADAP1	0,00636	0,990	0,990
GOTERM_MF_FAT	GO:0034450~ubiquitin-ubiquitin ligase activity	2	UBE4B, STUB1	0,02365	0,994	0,644
UP_SEQ_FEATURE	domain:EGF-like 5; calcium-binding	3	<b>NOTCH1, JAG2, MEGF6</b>	0,01542	0,998	0,959
INTERPRO	IPR003109:GoLoco motif	2	RGS12, GPSM1	0,03518	1,000	0,859
GOTERM_BP_FAT	GO:0030182~neuron differentiation	7	<b>NOTCH1, HES5, EFNA2, RXRA, JAG2, SPO2, DVL1</b>	0,01088	1,000	0,981
GOTERM_BP_FAT	GO:0048667~cell morphogenesis involved in neuron differentiation	5	<b>NOTCH1, EFNA2, RXRA, SPO2, DVL1</b>	0,01226	1,000	0,950
GOTERM_MF_FAT	GO:0005083~small GTPase regulator activity	5	ARFGAP1, ACAP3, RHPN1, ARHGEF16, ADAP1	0,04172	1,000	0,784
GOTERM_BP_FAT	GO:0048812~neuron projection morphogenesis	5	<b>NOTCH1, EFNA2, RXRA, SPO2, DVL1</b>	0,01307	1,000	0,909
INTERPRO	IPR002610:Peptidase S54, rhomboid	2	RHBDL1, RHBDL2	0,04501	1,000	0,867
INTERPRO	IPR003613:U box domain	2	UBE4B, STUB1	0,04501	1,000	0,867
GOTERM_BP_FAT	GO:0048663~neuron fate commitment	3	<b>NOTCH1, HES5, JAG2</b>	0,01394	1,000	0,870
UP_SEQ_FEATURE	domain:EGF-like 26	2	<b>NOTCH1, MEGF6</b>	0,02538	1,000	0,971
UP_SEQ_FEATURE	domain:EGF-like 20	2	<b>NOTCH1, MEGF6</b>	0,02538	1,000	0,971
UP_SEQ_FEATURE	domain:EGF-like 24	2	<b>NOTCH1, MEGF6</b>	0,02538	1,000	0,971
UP_SEQ_FEATURE	domain:EGF-like 27	2	<b>NOTCH1, MEGF6</b>	0,02538	1,000	0,971
GOTERM_BP_FAT	GO:0050909~sensory perception of taste	3	GNG13, TAS1R3, SCNN1D	0,01523	1,000	0,845
GOTERM_BP_FAT	GO:0032012~regulation of ARF protein signal transduction	3	ARFGAP1, ACAP3, ADAP1	0,01523	1,000	0,845
UP_SEQ_FEATURE	splice variant	49	<b>JAG2, FAM195A, GET4, ZYG11B, DPP8, BRD9, GMEB1, ARHGEF16, WDR90, WDR47, ACAP3, C16ORF13, HAGHL, CPSF3L, ARFGAP1, RHPN1, PUSL1, ABCA2, PRDM16, STUB1, ZBTB8OS, RGS12, PLCH2, MSLN, GPSM1, SCNN1D, C17ORF42, PHACTR4, SAMD11, UBE4B, SYCE1, ATAD5, DVL1, C9ORF142, SFPQ, JMJD8, NARFL, RHOT2, RHBDL1, CHTF18, CACNA1H, WDR24, RHBDL2, PLEKHN1, MEGF6, TMEM41B, CCDC78, COL20A1, ZBTB8A</b>	0,02825	1,000	0,948
GOTERM_BP_FAT	GO:0060120~inner ear receptor cell fate commitment	2	<b>HES5, JAG2</b>	0,01704	1,000	0,833
GOTERM_BP_FAT	GO:0009912~auditory receptor cell fate commitment	2	<b>HES5, JAG2</b>	0,01704	1,000	0,833
UP_SEQ_FEATURE	domain:EGF-like 22	2	<b>NOTCH1, MEGF6</b>	0,03038	1,000	0,921
GOTERM_BP_FAT	GO:0000902~cell morphogenesis	6	<b>NOTCH1, EFNA2, RXRA, SPO2, DVL1, IDUA</b>	0,01799	1,000	0,808
UP_SEQ_FEATURE	domain:U-box	2	UBE4B, STUB1	0,03535	1,000	0,916
UP_SEQ_FEATURE	domain:EGF-like 4	3	<b>NOTCH1, JAG2, MEGF6</b>	0,03572	1,000	0,882
GOTERM_BP_FAT	GO:0000904~cell morphogenesis involved in differentiation	5	<b>NOTCH1, EFNA2, RXRA, SPO2, DVL1</b>	0,02049	1,000	0,813
GOTERM_BP_FAT	GO:0048858~cell projection morphogenesis	5	<b>NOTCH1, EFNA2, RXRA, SPO2, DVL1</b>	0,02076	1,000	0,783
GOTERM_BP_FAT	GO:0032990~cell part morphogenesis	5	<b>NOTCH1, EFNA2, RXRA, SPO2, DVL1</b>	0,02394	1,000	0,799
GOTERM_BP_FAT	GO:0031175~neuron projection development	5	<b>NOTCH1, EFNA2, RXRA, SPO2, DVL1</b>	0,02394	1,000	0,799
UP_SEQ_FEATURE	zinc finger region:C4-type	3	ARFGAP1, ACAP3, ADAP1	0,04764	1,000	0,919
GOTERM_BP_FAT	GO:0032989~cellular component morphogenesis	6	<b>NOTCH1, EFNA2, RXRA, SPO2, DVL1, IDUA</b>	0,02728	1,000	0,813
GOTERM_BP_FAT	GO:0007409~axonogenesis	4	<b>NOTCH1, EFNA2, RXRA, SPO2</b>	0,04981	1,000	0,943

**Supplementary Table 9 – Fractions of mutation carriers and of cases with tumor-associated loss of SDHB in the subsets of paragangliomas analyzed for germline SDH mutations.** Germline SDH gene mutation analyses, performed in 34 cases for *SDHB*, *SDHD*, and *SDHC*, and in 9 cases for *SDHAF2*, identified 13 mutation carriers (38.2%), of which 5/34 (14.7%) in *SDHB*; 1/34 (2.9%) in *SDHC*; 6/34 (17.6%) in *SDHD*; 1/9 (11.1%) in *SDHAF2*. Furthermore, CNV and gene-centric analyses identified a large germline *SDHB* deletion in one additional case (17.1% of *SDHB* mutation carriers; 40% of total mutation carriers).

Mutation	Fraction with <i>SDHB</i> loss	Age (range, mean)	Gender
<i>SDHB</i>	6/35 (17.1%)	6/6 (100%)	25-55, 35,3
<i>SDHC</i>	1/34 (2.9%)	0/1 (0%)	43
<i>SDHD</i>	6/34 (17.6%)	5/6 (83,3%)	31-59, 47,5
<i>SDHAF2</i>	1/9 (11.1%)	1/1 (100%)	24
<b>Total Mutated</b>	<b>14/35 (40%)</b>	<b>12/14 (85,7%)</b>	<b>24-59, 45,6</b>
<b>Undetected</b>	<b>21/35 (60%)</b>	<b>6/20 (30%)</b>	<b>25-67, 45,8</b>

P=0,0019

**Supplementary Table 10 - Individual characteristics, SDH mutations, and loss of SDHB immunostaining in paraganglioma subsets with different clinical presentation.** SDHB loss was detected 9/11 multiple/recurrent paraganglioma (81.8%) and was less frequent in the tympano-jugular (9/28, 32.1%) and tympanic (1/4, 25%) tumors. The unique metastatic tumor (34PTJ) and the single vagal PGL (PV-06/R18) resulted SDHB-negative.

Presentation	Age (range, mean) (46 cases)	Gender (46 cases)	Fraction with <i>SDH</i> mutations (35 cases)*	Fraction with <i>SDHB</i> loss (45 cases)†
<b>multiple/recurrent (11)</b>	25-59, 43.7	6F, 5M	7/10 (70%)	9/11 (81.8%)
<b>metastatic</b>	25	1F	1/1 (100%)	1/1 (100%)
<b>tympano-jugular (29)</b>	24-67, 45.8	18F, 11M	5/23 (21.7%)	9/28 (32.1%)
<b>tympanic (4)</b>	58-73, 58.7	3F, 1M	na	1/4 (25%)
<b>vagal (1)</b>	27	1F	1/1 (100%)	1/1(100%)
<b>total cases (46)</b>	<b>24-73, 45.6</b>	<b>29F, 17M</b>	<b>14/35 (40%)</b>	<b>21/45 (46.6%)</b>

\*Cases with known mutation status in *SDH* genes;

†SDHB immunohistochemistry not assessable for one case due to poor sample quality.

**Supplementary Table 11** - Mean NOTCH1 and JAG2 immunostaining intensities ( $\pm$  SD) in chief cells (CC), sustentacular cells (SC) and endothelial cells (EC) of paraganglioma subsets defined according to *SDH* mutation status (detected, undetected) and to SDHB immunohistochemistry (IHC, negative or positive). Endothelial cells are negative for JAG2.

	NOTCH1 IHC intensity ( $\pm$ SD)			<i>P</i>	JAG2 IHC intensity ( $\pm$ SD)		<i>P</i>
	CC	SC	EC		CC	SC	
<b><i>SDH</i> mutation</b>							
<b>detected (14)</b>	1.76 (0.43)	1.90 (0.43)	2.76 (0.43)	ns	1.00 (0.32)	1.20 (0.52)	ns
<b>undetected (21)</b>	1.78 (0.42)	1.92 (0.61)	2.78 (0.42)	ns	0.78 (0.42)	0.92 (0.61)	ns
<b>SDHB IHC</b>							
<b>negative (21)</b>	1.76 (0.44)	1.95 (0.50)	2.76 (0.44)	ns	0.9 (0.44)	1.15 (0.74)	ns
<b>positive (24)</b>	1.91 (0.51)	2.04 (0.64)	2.78 (0.42)	ns	1.00 (0.31)	1.23 (0.53)	ns